Cholesterol Metabolism

Objectives

- Understand the structure and functions of cholesterol
- Discuss the regulation of cholesterol homeostasis in the body
- Comprehend the important steps of cholesterol synthesis pathway
- Identify different levels of regulation of cholesterol synthesis
- Discuss the association of hypercholesterolemia with abnormal cholesterol metabolism
- Understand the role of statins in the treatment of hypercholesterolemia

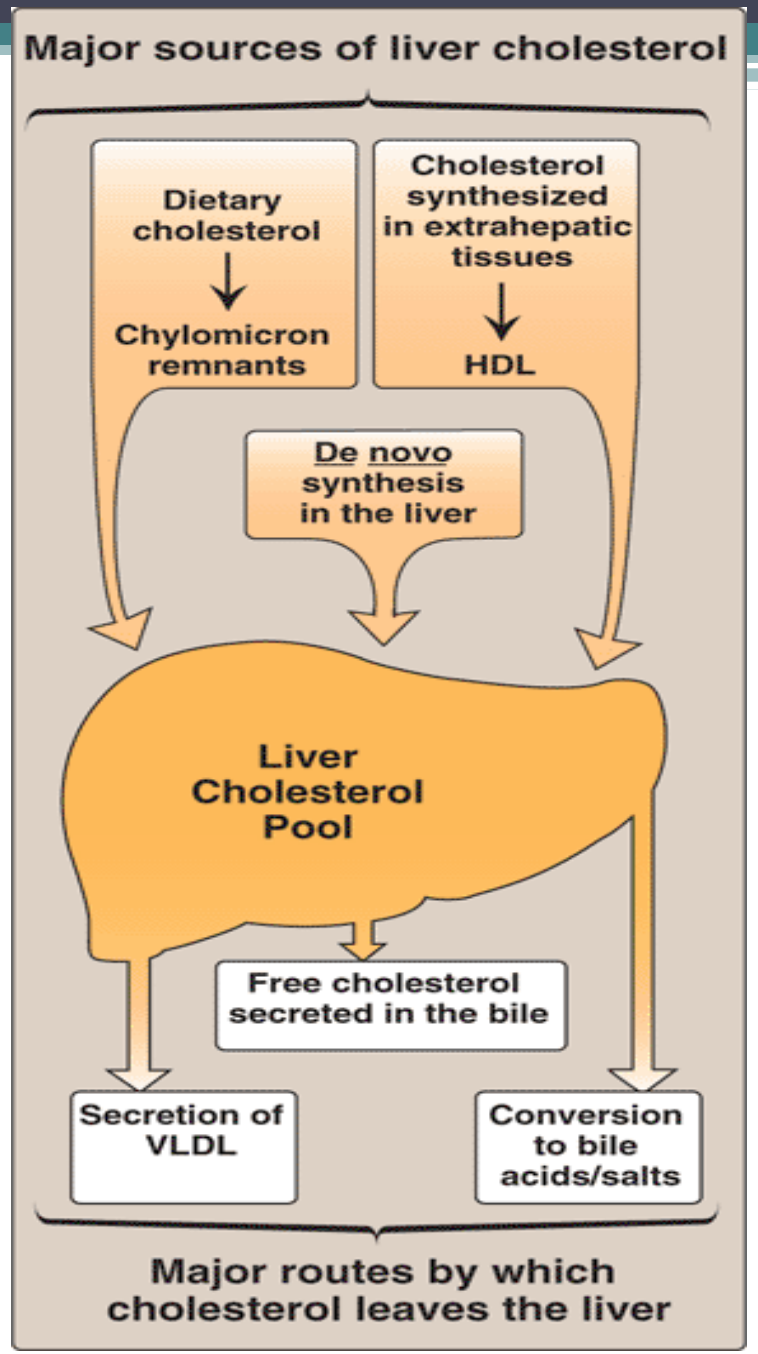
Overview

- Introduction
- Cholesterol structure
- Cholesteryl esters
- Cholesterol synthesis
- Rate limiting step
- Regulation of cholesterol synthesis
- Regulation of HMG CoA reductase
- Excretion of cholesterol
- Hypercholesterolemia and treatment

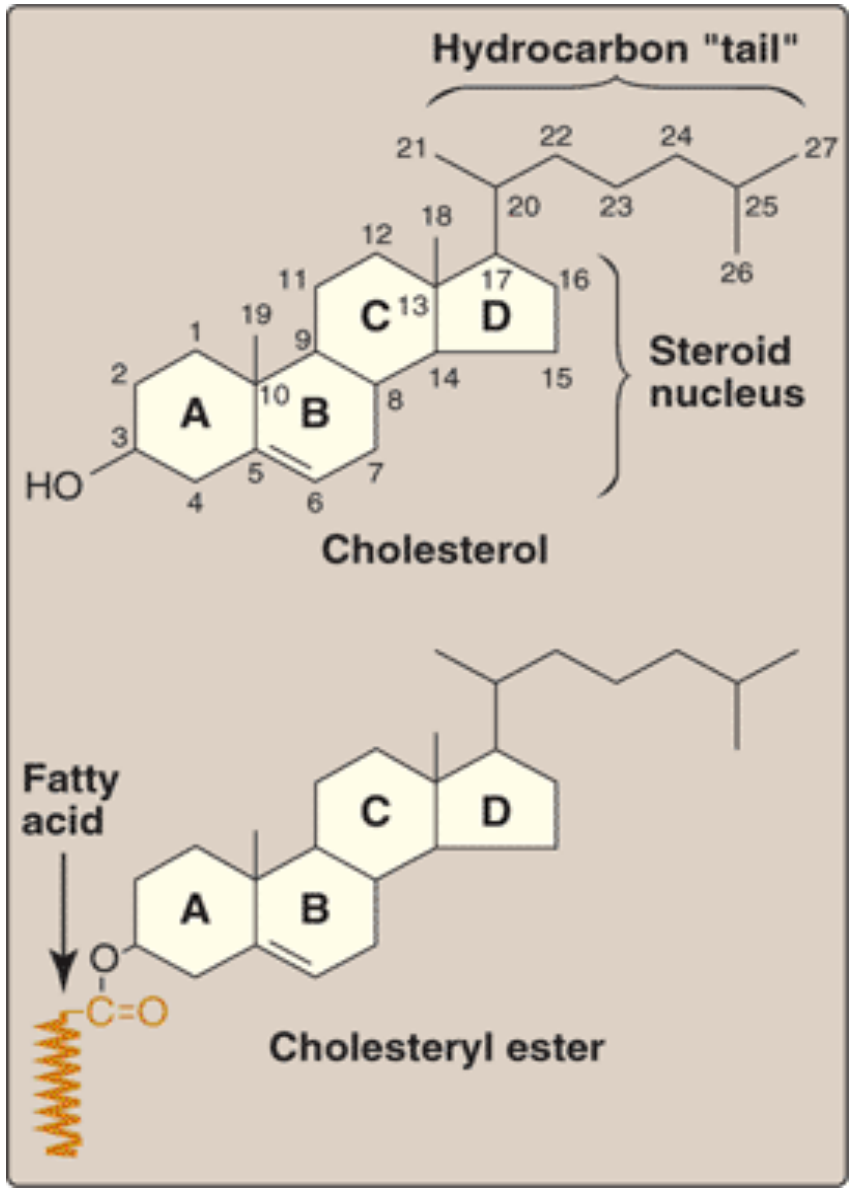
Cholesterol

- Most important animal steroid
- Maintains membrane fluidity
- Insulating effect on nerve fibres
- Cholesterol is the parent molecule for
  - Bile acids and bile salts
  - Steroid hormones
  - Vitamin D_3

Liver plays a central role in the regulation of cholesterol homeostasis



Cholesterol Structure



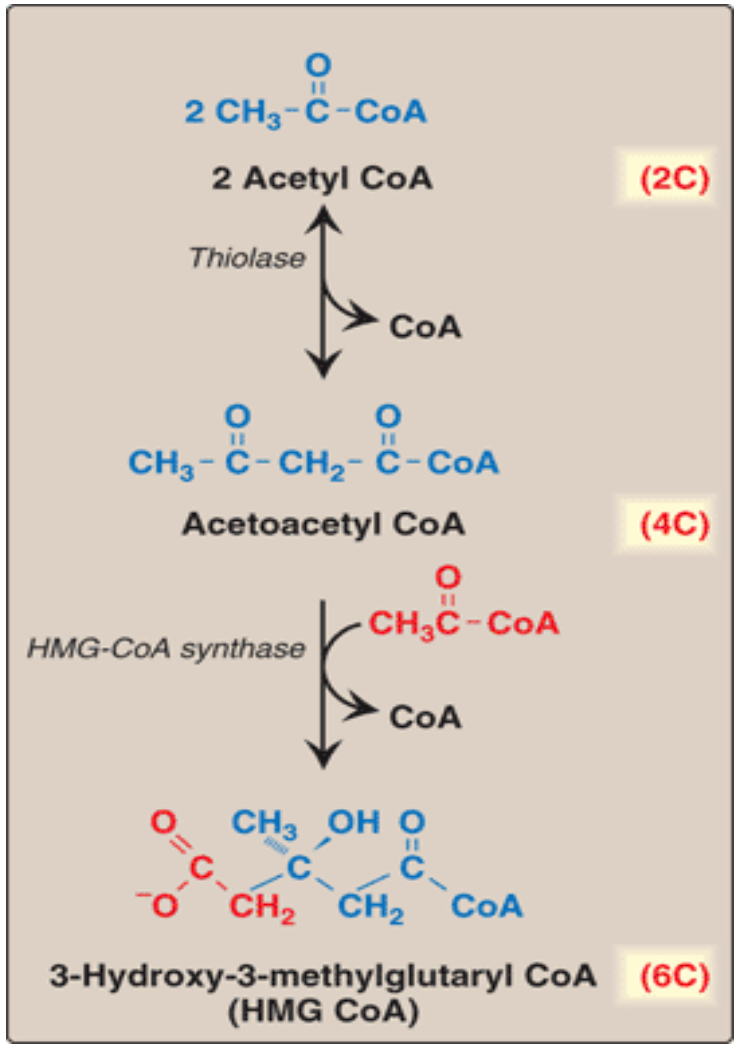
Cholesteryl esters

- Most plasma cholesterol is esterified with a fatty acid
- CEs are not present in membranes
- Present in small amounts in most cells
- More hydrophobic than cholesterol

Cholesterol synthesis

- Synthesized in all tissues
- Major sites for synthesis: liver, adrenal cortex, testes, ovaries and intestine
- All carbon atoms are derived from acetyl CoA
- Enzymes involved in biosynthesis are partly located in ER and partly in cytoplasm

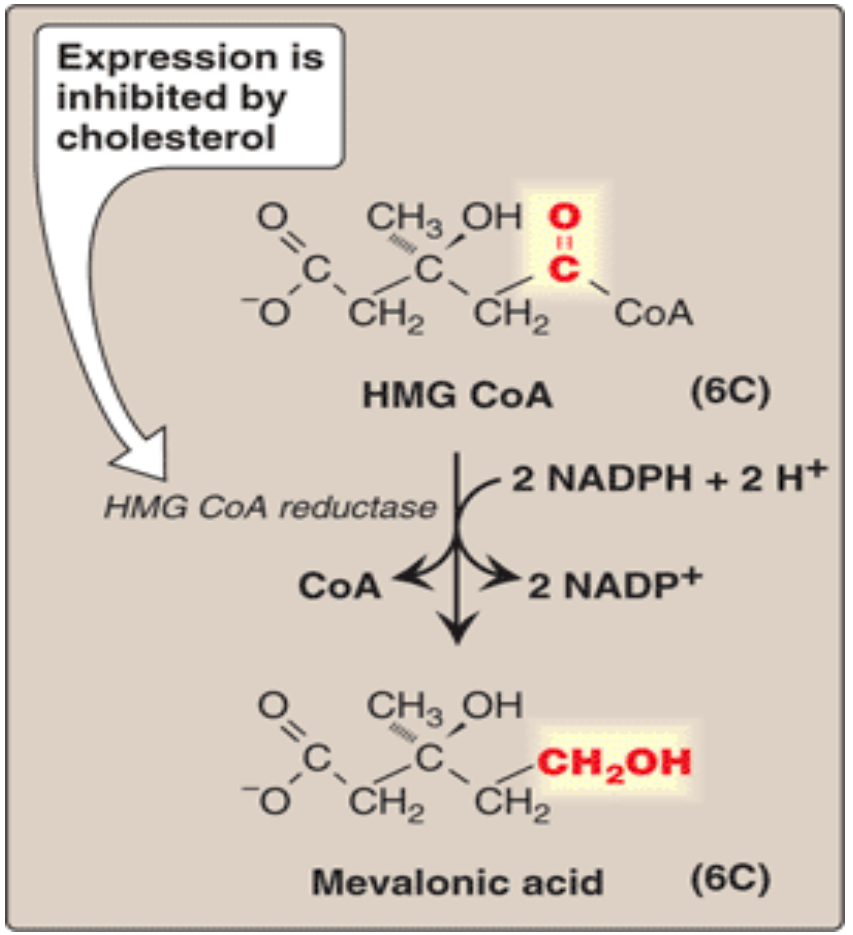
Synthesis of HMG CoA



- HMG CoA synthase is present in both cytosol and mitochondria of liver
- Mitochondrial-ketogenesis
- Cytosolic – cholesterol synthesis

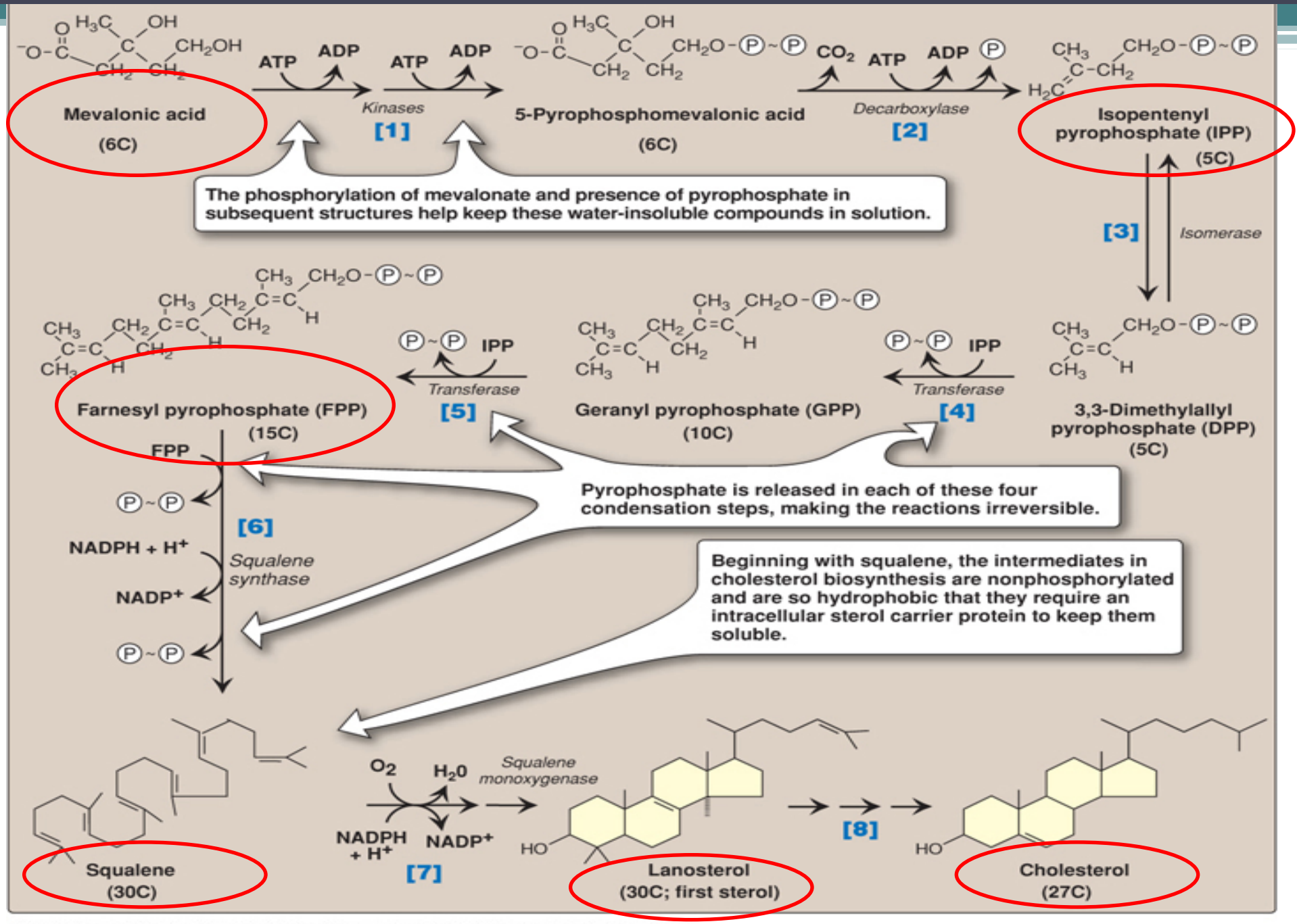
Synthesis of mevalonic acid

- Rate limiting and key step
- Occurs in cytosol
- HMG CoA reductase is an ER membrane enzyme with catalytic unit hanging in the cytosol



Further steps in synthesis

- Production of a 5-carbon unit:
  - Isopentinyl pyrophosphate (IPP)
- Condensation to a 30C compound: squalene
- Cyclization of squalene to 30C lanosterol
- Synthesis of 27-Carbon cholesterol (defect in this leads to Smith-Lemli-Opitz Syndrome)


Mevalonic acid
(6C)
ATP
ADP
ATP
ADP
Kinases
[1]
5-Pyrophosphomevalonic acid
(6C)
CO2
ATP
ADP
Decarboxylase
[2]
Isopentenyl pyrophosphate (IPP)
(5C)
The phosphorylation of mevalonate and presence of pyrophosphate in subsequent structures help keep these water-insoluble compounds in solution.
[3]
Isomerase
Farnesyl pyrophosphate (FPP)
(15C)
IPP
Transferase
[5]
Geranyl pyrophosphate (GPP)
(10C)
IPP
Transferase
[4]
3,3-Dimethylallyl pyrophosphate (DPP)
(5C)
FPP
[6]
NADPH + H+
NADP+
Squalene synthase
Pyrophosphate is released in each of these four condensation steps, making the reactions irreversible.
Beginning with squalene, the intermediates in cholesterol biosynthesis are nonphosphorylated and are so hydrophobic that they require an intracellular sterol carrier protein to keep them soluble.
Squalene
(30C)
O2
H2O
NADPH + H+
NADP+
[7]
Squalene monoxygenase
Lanosterol
(30C; first sterol)
[8]
Cholesterol
(27C)

Regulation of Cholesterol Synthesis

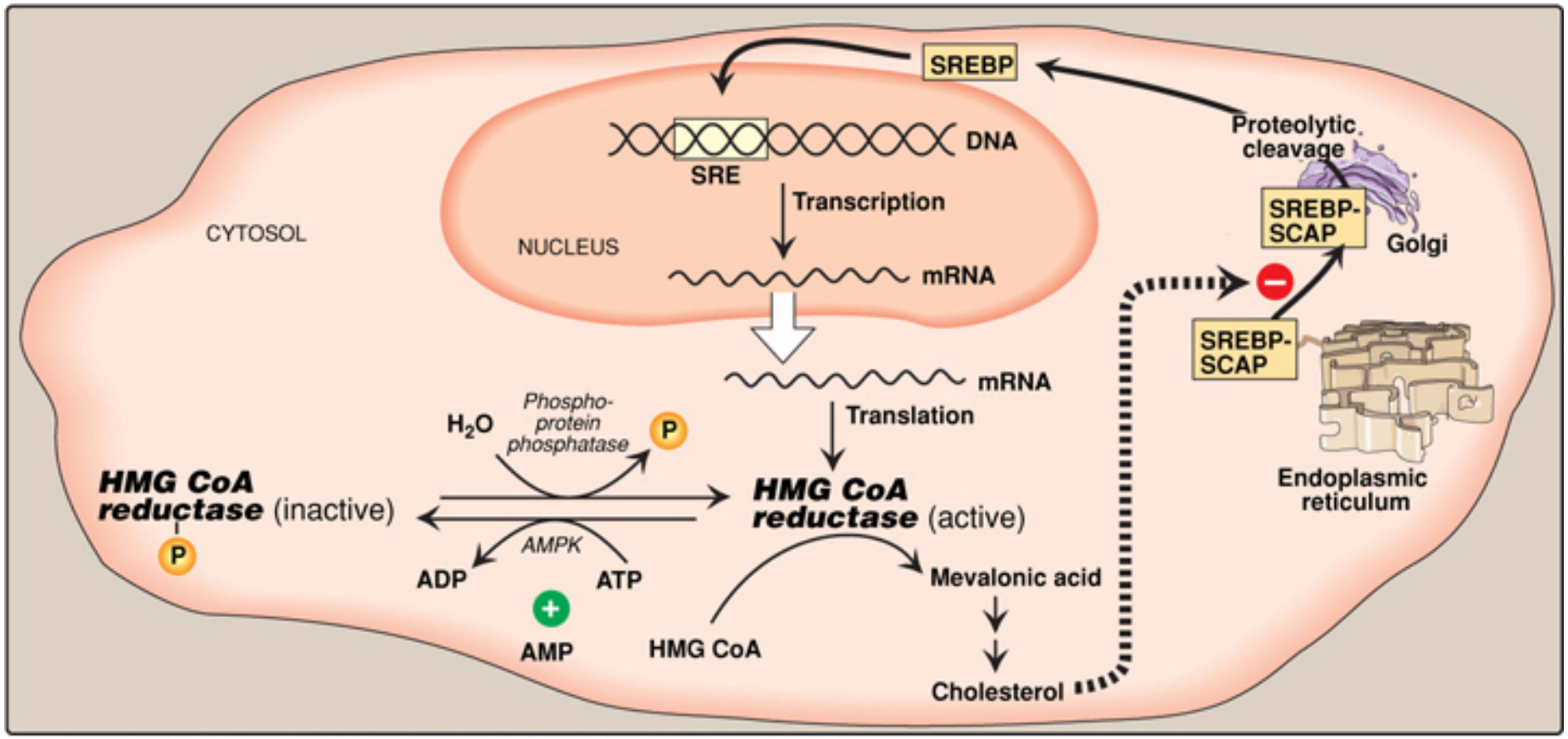
- HMG CoA reductase is the rate-limiting enzyme of cholesterol synthesis

HMG CoA Reductase Regulation

- Sterol-dependent regulation of gene expression
- Sterol-accelerated enzyme degradation
- Sterol-independent phosphorylation/ dephosphorylation
- Hormonal regulation

Sterol-dependent regulation of gene expression of HMG CoA

- When sufficient cholesterol is present, transcription is suppressed and vice versa
- Sterol Regulatory Element (SRE) is a recognition sequence in the DNA
- SREBP (SRE binding protein) binding to SRE is essential for transcription of this gene
- SREBP cleavage-activating protein (SCAP) is an intracellular cholesterol sensor



Sterol-dependent regulation

Cholesterol High

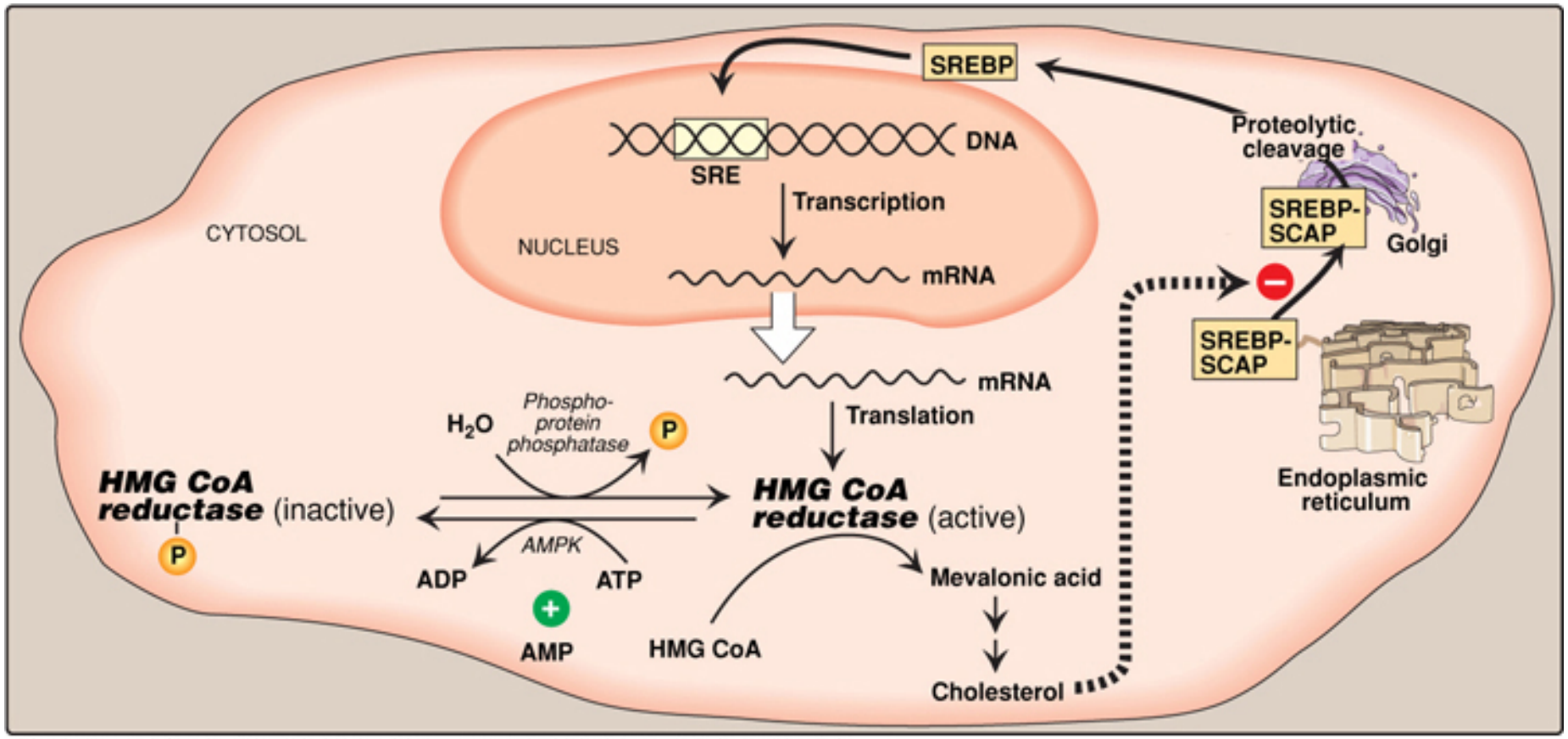
- SCAP binds to insig protein (insulin-induced protein) in ER membrane
- SCAP-SREBP is retained in the ER
- Down regulation of cholesterol synthesis

Cholesterol Low

- SCAP-SREBP moves to Golgi bodies
- SCAP is removed from SREBP
- SREBP binds to SRE in DNA
- HMG CoA gene is activated

Enzyme phosphorylation and dephosphorylation

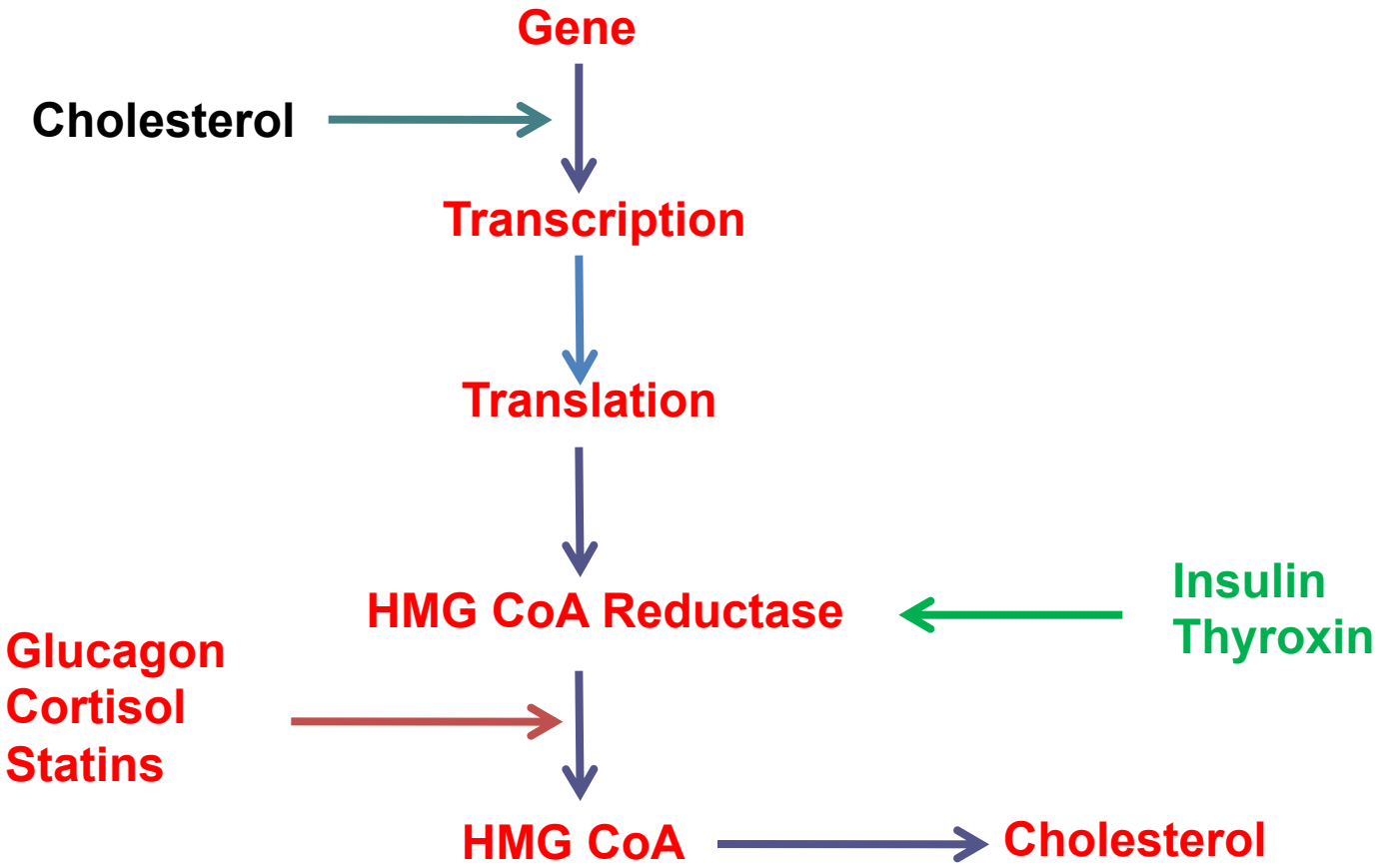
- AMP- activated protein kinase (AMPK) for phosphorylation
- Phosphorylated form of enzyme is inactive
- Dephosphorylated form is active
- Low ATP or High AMP → cholesterol synthesis decreases



Hormonal Regulation

- Insulin and thyroxine increase upregulation of enzyme expression
- Glucagon and cortisol have opposite effect

HMG CoA Reductase Regulation



Excretion of cholesterol

- By conversion into bile acids and bile salts- excreted in the feces
  - Secretion of cholesterol in bile
  - Transported to intestine for elimination
- In the intestine, some cholesterol is converted by bacteria into coprostanol and cholestanol before excretion

Hypercholesterolemia

- High conc. of cholesterol in blood
- Leads to atherosclerosis
- Statin drugs are used to decrease plasma cholesterol levels
- Statins are structural analogs of HMG CoA reductase
- Statins inhibit enzyme activity by competitive inhibition

β-Sitosterols/ Phytosterols

- Plant sterols are poorly absorbed by humans
- Block the absorption of dietary cholesterol
- Clinically useful in the dietary treatment of hypercholesterolemia

Take home message

- Cholesterol is important various body functions
- Liver plays a major role in the cholesterol homeostasis in the body
- HMG CoA reductase is a rate-limiting enzyme for cholesterol synthesis

References

- Lippincott's Biochemistry 5th Edition, Chapter 18, pp 219–224